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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,825	11/18/2003	Gregory Stephanopoulos	MIN-P01-042	7074

28120 7590 11/18/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,825	STEPHANOPOULOS ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008 and 11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10,12-28 and 33-37* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 12-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,8-10 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2008 has been entered.

Status of the Claims

2. The amendment received on October 2, 2006 canceled claim 7.

The amendment to the claims received on September 20, 2007 amended claims 1, 8, and 9 and canceled claim 11.

The amendment to the claims received on May 30, 2008 and entered on August 11, 2008 amended claims 1 and 8, canceled claims 9 and 29-32, and added new claims 33-37.

Claims 1-6, 8, 10, 12-28, and 33-37 are currently pending.

Claims 1, 5-6, 8, 10, and 33-37 are currently under consideration.

Election/Restrictions

3. Applicants elected, with traverse, Group I (previous claims 1-11) in the reply filed on October 2, 2006. Claims 12-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

4. Applicants' election without traverse of mRNA as the species of expression level in the reply filed on October 6, 2006 is reiterated. Claims 2-4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 6, 2006.

Priority

5. The present application (10/716,825, filed November 18, 2003) claims status as a CIP of U.S. application 10/060,048 filed January 29, 2002 and claims benefit of U.S. provisional application 60/427,265 filed November 18, 2002.

6. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, provisional Application Nos. 60/427,265 and 10/060,048, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. U.S. provisional applications 60/427,265 and 10/060,048 do not teach SEQ ID NOs: 1-43. Therefore, the present claims have a priority date of November 18, 2003 (i.e. filing date of the present applicantion).

Invention as Claimed

7. Independent claim 1: A method for diagnosing an oral cancer in a patient comprising: (a) obtaining a biological sample from a patient, (b) determining the expression level of a plurality of genes associated with an oral cancer in the biological sample, thereby producing a test expression profile wherein the plurality of genes are at least 40 genes selected form SEQ ID NOs: 1-43, and (c) comparing the test expression profile with at least one signature expression profile from a patient known to have an oral cancer wherein said signature expression profile consists said plurality of genes and is indicative of an oral cancer wherein if the test expression profile substantially matches said signature expression profile the patient has the oral cancer and variations thereof.

Independent claim 33: A method for diagnosing an oral cancer in a patient comprising: (a) obtaining a biological sample form a patient, (b) determining the expression level of a plurality of genes associated with an oral cancer in the biological sample thereby producing a test expression profile wherein the plurality of genes consist of at least 5 genes selected form SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40, and (c) comparing the test expression profile with at least one signature expression profile form a patient known to have an oral cancer wherein said signature expression profile consists of said plurality of genes and is indicative of an oral cancer wherein if the test expression profile substantially matches said signature expression profile the patient has the oral cancer and variations thereof.

Sequence Compliance

8. The application is presently in compliance with the sequence rules.

Withdrawn Rejections

9. The rejection of claims 1, 5-6, and 8-10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the claim amendments received on May 30, 2008.

10. The rejection of claims 1, 5-6, and 8-10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding Table 1 is withdrawn in view of the claim amendments received on May 30, 2008.

11. The rejection of claims 8-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments received on May 30, 2008.

12. The rejection of claims 1, 5-6, and 8-10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments received on May 30, 2008.

13. The rejection of claims 1, 5-6, and 8-10 under 35 U.S.C. 102(e) as being anticipated by Katz et al. U.S. Patent 6,797,471 filing date of August 6, 2001 and effective filing date of August 4, 2000 is withdrawn in view of the claim amendments received on May 30, 2008.

14. The rejection of claims 1, 5-6, and 8-10 under 35 U.S.C. 102(e) as being anticipated by Warrington et al. U.S. Patent 7,108,969 filing date of September 10, 2001 and effective filing date of September 8, 2000 is withdrawn in view of the claim amendments received on May 30, 2008.

New Rejections

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1, 5-6, 8, 10, and 33-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

Applicants point to page 12, lines 10-19; page 71, lines 3-5 and 17-19; Table 1, pages 79-81; and claims 1 and 9 for support of the various claim amendments received on May 30, 2008. In addition, applicants state that only 43 sequences have been provided because "two genes of Table 1 (i.e., accession numbers: HG3549-HT3751 and HG2992-HT5186) are not included in

the sequence listing since applicants have not retrieved the sequences of these two genes and cannot assign a sequence identifier to each of these two genes" (see page 2, last paragraph of the response received on August 11, 2008).

Page 12, lines 10-19: In an alternative embodiment, a subset of the 45 I-IPE genes may be used to diagnose an oral disease. A subset of these 45 genes useful for oral cancer diagnosis may be further identified by applying the statistical methods described in the Exemplification section to oral cancer samples and normal samples. The expression profile of the subset of genes may provide a disease signature useful for diagnostic and prognosis purposes. For example, the subset of genes may be less than 20 genes, less than 10 genes, or less than 5 genes. In any case, a subset of genes may be selected, and optionally a corresponding data set of expression levels, rank or concentration, that may be employed to diagnose or detect the indication of interest.

Page 71, lines 2-5 and 16-20: This is exactly what is observed with the expression data of oral epithelium cancer, as shown in Figure 5b. Clearly, 40-45 genes are sufficient to accurately predict the class of the samples in the test set and, as such, they are deemed most discriminatory of the oral epithelium cancerous state.

As an additional validation step of the experimental and computational methods used in deriving these results, we selected three genes from Table 1 whose expressions are consistently altered in the 5 paired cases of oral cancer and applied real-time quantitative PCR (RT-QPCR) to independently measure their expression levels.

Table 1: refers to genes via accession number, gene name, chromosome location, and function. No sequences were present at the time of filing.

Therefore, the specification as originally filed does not provide support for the specific sequences of SEQ ID NOs: 1-43 (see present claims 1, 8, 33, and 36), an open ended range of "at least 40 genes" (see present claim 1), a random subset of 40 genes from the group consisting of SEQ ID NOs: 1-43 (see present claim 1) which is diagnostic, a subset of SEQ ID NOs: 1-43 (see present claim 8), an open-ended range of "at least 5 genes" (see present claim 33), a random subset of 5 genes from the group consisting of SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40 (see present claim 33) which is diagnostic, a subset of SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40 which is diagnostic (see present claim 36), and "comparing the test expression profile with at least one signature expression profile form a

patient known to have an oral cancer" (see present claims 1 and 33). Applicants have not provided evidence that the specific sequences of SEQ ID NOs: 1-43 were associated with the accession numbers, gene names, chromosome locations, or functions in originally disclosed Table 1 at the time of filing.

Applicants are respectfully directed to MPEP § 2163.05, section III regarding ranges.

In addition, it is noted that the "diagnostic subset" in new claims 33-37 appears to have been crafted to overcome the art rejections of record and is not a specific subset disclosed in the originally filed specification. Therefore, applicants are respectfully requested to specifically point out support for the subset in new claims 33-37.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1, 5-6, 8, 10, and 33-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention.

A. Regarding "wherein the plurality of genes are at least 40 genes selected from SEQ ID NOs: 1-43", can the plurality of genes contain more than 43 genes? Regarding "wherein the plurality of genes consist of at least 5 genes selected from SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40", can the plurality of genes contain more than 14 genes listed? If so, what are the other genes and are they necessary for diagnosis? The "at least 40 genes" and "at

least 5 genes" are an open-ended ranges that encompasses any group comprising more than 5 or more than 40 genes.

B. Regarding SEQ ID NOS: 1-43, is the full-length sequence required or only part of the sequence (i.e. mutations, etc. included), can 5' and 3' additions be present, etc.?

C. Regarding present claim 8, are all 43 sequences of SEQ ID NOs: 1-43 required by the claims or are subsets included? Can additional genes be added to the plurality?

D. Regarding claim 33, the limitation "the plurality of genes consist of at least 5 genes selected form SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40", the claim is both open (i.e. at least 5 genes) and closed (i.e. consist). Therefore, the scope of the claim is not clear. Applicants are respectfully directed to MPEP § 2173.05(h), section I regarding Markush type language.

E. Regarding claim 1, the limitations "at least 40" and "said signature expression profile consists of said plurality of genes", the claim is both open (i.e. at least 40 genes) and closed (i.e. consists). Therefore, the scope of the claim is not clear. Applicants are respectfully directed to MPEP § 2173.05(h), section I regarding Markush type language.

F. Regarding present claim 36, are all 14 sequences of SEQ ID NOs: 3, 5, 10, 15, 16, 21, 22, 27, 28, 31, 32, 35, 37, and 40 required by the claims or are subsets included? Can additional genes be added to the plurality?

Maintained Rejections

19. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

20. Claims 1, 5-6, 8, 10, and 33-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an **enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The presently claimed invention is drawn to a method for diagnosing an oral cancer in a patient comprising: (a) obtaining a biological sample, (b) determining the expression level of a

plurality of genes associated with an oral cancer in the biological sample, thereby producing a test expression profile wherein the plurality of genes are at least 5 genes selected from SEQ ID NOs: 1-43, and (c) comparing the test expression profile with at least one signature expression profile of the plurality of genes is indicative of an oral cancer and variations thereof. Therefore, the presently claimed invention does not specify the minimum number or genes or the specific subset of genes necessary for diagnosis. In addition, the limitations of biological sample and oral cancer encompass broad genuses.

The present specification merely states that of the various genes analyzed via GeneChip® array, the samples from five oral cancer patients (type, stage, etc. not specified) varied in 45 genes wherein 30 genes were "downregulated" and 15 of genes were "upregualted" (please refer to pages 69 and 72-73). The specification does not provide information regarding the level of upregualtion or downregulation compared to control (e.g. normal, noncancerous sample). Accordingly, the claim scope is unduly broad with respect to encompassed genes and expression profiles.

The state of the prior art and the level of predictability in the art:

Diagnosis of oral cancer via altered gene expression is highly unpredictable, particularly in humans. Rosas et al. (Cancer Research 61: 939-942, 2001) teach that gene expression levels may not be altered, but rather methylation of the genes and only 23-56% of patients with head and neck primary tumors had hypermethylated genes (e.g. levels not conclusive for diagnostic purposes; please refer to abstract, Results, and Discussion sections). Liao et al. (Oral Oncology 36: 272-276, 2000) teach that 62.5% of patients with oral squamous cell carcinoma were positive for p53 mutations while 18.52% of samples from healthy patients had p53 mutations (e.g. not

conclusive for diagnostic purposes; please refer to abstract and Discussion section). Furthermore, Williams (Journal of Clinical Pathology 53: 165-172, 2000) teach that oral squamous carcinogenesis is a multistep process involving multiple genetic events wherein not all genetic events occur in all squamous oral carcinogenesis or similar genetic alteration may occur at different times (please refer to abstract and Conclusion section).

In addition, Scully et al., 2000, Genetic aberrations in oral or head and neck squamous cell carcinoma 3: clinico-pathological applications, Oral Oncology, 36: 404-413 teach that suspected markers are not always predictive (i.e. diagnostic) including p53 and microsatellite instability at chromosomes 3p, 6p, 7q, 9p, 11p, and 11q (please refer to section 5.1). Furthermore, Schwartz, 2000, Biomarkers and Molecular Epidemiology and Chemoprevention of Oral Carcinogenesis, Crit. Rev. Oral Biol. Med, 1191): 92-122 teach that potential biomarkers must go through rigorous experimentation in order to have confidence in the ability of the biomarker(s) to define relative risk including animal model studies, expression of the marker in a staged transformation assay, expression of the marker in early pre-malignant human biopsies from a high risk group, and utilizing a large clinical population (see section III particularly subsection B). Moreover, Alevizos et al., 2001, Oral cancer in vivo gene expression profiling assisted by laser capture microdissection and microarray analysis, Oncogene, 20: 6196-6204 found 39 genes that were changed in 5 of 5 cases associated with oral cancer wherein some of the genes are not associated with present SEQ ID NOs: 1-43 (D86983 for example) and all 43 of the presently claimed genes are not associated with oral cancer (see Table 1). Additionally, Alevizos et al. discuss the differences between their results and two other studies (Shillitoe et al. and Leethanakul et al.) and suggest that the differences are reflective of different experimental approaches and methods

of analysis (see pages 6200-6201). Therefore, which of the four different studies have actually found viable biomarkers for diagnosis? Hwang et al., 2003, Genomic dissection for characterization of cancerous oral epithelium tissues using transcription profiling, Oral Oncology, 39: 259-268 (provided by applicants in the IDS; NPL of present invention) teach that a large sampling size should be performed to validate the credibility of the identified discriminatory genes, the samples size presently utilized is not large enough to allow for statistically significant subclassification according to clinical characterization, and suggests examining the effect of each factor on disease phenotype to fully understand the role of the gene in disease (see page 267).

Aris et al., 2004, Noise filtering and nonparametric analysis of microarray data underscores discriminating markers of oral, prostate, lung, ovarian, and breast cancer, BMC Bioinformatics, 5: 185-193 teach the potential issues of relying on Affymetrix GeneChip™ data for determining diagnostic markers for oral cancer including false positives (e.g. absence of error modeling 1,730 genes identified in oral cancer, with error modeling 129 genes identified in oral cancer; please refer to the abstract; Cancer-specific Biomarkers section). Hwang et al., 2002, Determination of minimum sample size and discriminatory expression patterns in microarray data, Bioinformatics, 18(9): 1184-1193 teach the importance of determining a minimum sample size when analyzing microarray data to determine statistical reliability (see abstract; pages 1189, 1191-1193). Stephanopoulos et al., 2002, Mapping physiological states from microarray expression measurements, Bioinformatics, 18(8): 1054-1063 teach that application of different classification methods may point to different genes, therefore, it is important especially for

making conclusions regarding sample diagnosis to utilize multiple methods (see abstract; page 1062).

Therefore, the level of predictability in the art is dependent on many factors including data interpretation, statistical analysis, animal models (e.g. wherein animal knockouts could provide more definitive evidence), long-term studies (e.g. following patients throughout course of disease to determine if gene expression is altered), etc. While finding genetic markers to accurately diagnose oral cancer is important, the state of the art requires vast amounts of data including correlation of the gene to cancer with high probability, potentially finding one or more genetic markers for each oral cancer, detailed statistical analysis of data, etc. In addition, a showing that the genetic markers are specific for oral cancer and modulation is not associated with other diseases is required.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

There are no specific examples directed to the intended use language of the presently claimed invention (i.e. diagnosing oral cancer in patients), nor is there any information provided regarding correlating the altered gene expression data provided in the specification and diagnosing oral cancer. The specification contains only cursory statements that various genes are "down" or "up" in cancer (please refer to Table 1).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to facilitate clinical studies with large numbers of patients suffering from each known oral cancer and screen the entire genome to determine if any genes may be correlated to cancer, determine which sequences are relevant to the genes of SEQ ID NOs: 1-43, follow patients for years to determine if gene expression changes during the course of cancer, provide detailed statistical analysis of the data to limit potential false positives/negatives, etc.

Arguments and Response

21. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (enablement), for claims 1, 5-6, 8, 10, and 33-37 were considered but are not persuasive for the following reasons.

Applicants contend that SEQ ID NOs: 1-43 negate the scope of enablement rejection, the specification provides a working example to show that all the genes in Table 1 were differentially expressed in oral cancer patients and as such one of skill in the art would know that the expression profile of a specific subset of genes in Table 1 could be successfully used for diagnosis of an oral cancer, and the technique utilized for expression profiling are well known in the art.

Applicants' arguments are not convincing for the reasons of record. The addition of SEQ ID NOs: 1-43 does not negate the scope of enablement rejection. The working examples on pages 69-80 state that the "45 genes are strongly correlated with the appearance of malignancy in

oral epithelium" (page 69,lines 9-10) and "the 45 genes…exhibit close association with oral cancer development" (page 72, lines 27-28). It is noted: that only 43 sequences or less are present in the claims. Pages 69-80 of the present specification caution that diagnosis requires (1) determining which genes are relevant to disease and (2) determining a gene pattern that is a marker of a physiological state, but also questions whether the patterns can be utilized to diagnose cells or tissue samples (please refer to the paragraph spanning pages 69-70). In addition, it is noted that applicants have tested a very small number of samples (i.e. five patients) in determining that SEQ ID NOs: 1-43 are "diagnostic". In addition, a specific subset of genes or a minimum number of specific genes that are diagnostic are not provided in the original specification. While techniques for expression profiling (i.e. screening for gene expression) are well known in the art, specific genetic markers to diagnose oral cancer are not well known in the art. Thus, applicants are enabled for screening for gene expression, but have not provided an enabling disclosure for diagnosing oral cancer.

Diagnosis of oral cancer via altered gene expression is highly unpredictable, particularly in humans. Rosas et al. (Cancer Research 61: 939-942, 2001) teach that gene expression levels may not be altered, but rather methylation of the genes and only 23-56% of patients with head and neck primary tumors had hypermethylated genes (e.g. levels not conclusive for diagnostic purposes; please refer to abstract, Results, and Discussion sections). Liao et al. (Oral Oncology 36: 272-276, 2000) teach that 62.5% of patients with oral squamous cell carcinoma were positive for p53 mutations while 18.52% of samples from healthy patients had p53 mutations (e.g. not conclusive for diagnostic purposes; please refer to abstract and Discussion section). Furthermore, Williams (Journal of Clinical Pathology 53: 165-172, 2000) teach that oral squamous

carcinogenesis is a multistep process involving multiple genetic events wherein not all genetic events occur in all squamous oral carcinogenesis or similar genetic alteration may occur at different times (please refer to abstract and Conclusion section).

In addition, Scully et al., 2000, Genetic aberrations in oral or head and neck squamous cell carcinoma 3: clinico-pathological applications, Oral Oncology, 36: 404-413 teach that suspected markers are not always predictive (i.e. diagnostic) including p53 and microsatellite instability at chromosomes 3p, 6p, 7q, 9p, 11p, and 11q (please refer to section 5.1). Furthermore, Schwartz, 2000, Biomarkers and Molecular Epidemiology and Chemoprevention of Oral Carcinogenesis, Crit. Rev. Oral Biol. Med, 1191): 92-122 teach that potential biomarkers must go through rigorous experimentation in order to have confidence in the ability of the biomarker(s) to define relative risk including animal model studies, expression of the marker in a staged transformation assay, expression of the marker in early pre-malignant human biopsies from a high risk group, and utilizing a large clinical population (see section III particularly subsection B). Moreover, Alevizos et al., 2001, Oral cancer in vivo gene expression profiling assisted by laser capture microdissection and microarray analysis, Oncogene, 20: 6196-6204 found 39 genes that were changed in 5 of 5 cases associated with oral cancer wherein some of the genes are not associated with present SEQ ID NOs: 1-43 (D86983 for example) and all 43 of the presently claimed genes are not associated with oral cancer (see Table 1). Additionally, Alevizos et al. discuss the differences between their results and two other studies (Shillitoe et al. and Leethanakul et al.) and suggest that the differences are reflective of different experimental approaches and methods of analysis (see pages 6200-6201). Therefore, which of the four different studies have actually found viable biomarkers for diagnosis? Hwang et al., 2003,

Genomic dissection for characterization of cancerous oral epithelium tissues using transcription profiling, Oral Oncology, 39: 259-268 (provided by applicants in the IDS; NPL of present invention) teach that a large sampling size should be performed to validate the credibility of the identified discriminatory genes, the samples size presently utilized is not large enough to allow for statistically significant subclassification according to clinical characterization, and suggests examining the effect of each factor on disease phenotype to fully understand the role of the gene in disease (see page 267).

Aris et al., 2004, Noise filtering and nonparametric analysis of microarray data underscores discriminating markers of oral, prostate, lung, ovarian, and breast cancer, BMC Bioinformatics, 5: 185-193 teach the potential issues of relying on Affymetrix GeneChip™ data for determining diagnostic markers for oral cancer including false positives (e.g. absence of error modeling 1,730 genes identified in oral cancer, with error modeling 129 genes identified in oral cancer; please refer to the abstract; Cancer-specific Biomarkers section). Hwang et al., 2002, Determination of minimum sample size and discriminatory expression patterns in microarray data, Bioinformatics, 18(9): 1184-1193 teach the importance of determining a minimum sample size when analyzing microarray data to determine statistical reliability (see abstract; pages 1189, 1191-1193). Stephanopoulos et al., 2002, Mapping physiological states from microarray expression measurements, Bioinformatics, 18(8): 1054-1063 teach that application of different classification methods may point to different genes, therefore, it is important especially for making conclusions regarding sample diagnosis to utilize multiple methods (see abstract; page 1062).

Conclusion

22. If the present claims were amended to a method of screening biological samples for gene expression of SEQ ID NOs: 1-43 without any intended use as a means for diagnosing oral cancer, the claims would be enabled.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is (571)272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Amber D. Steele/
Patent Examiner, Art Unit 1639

November 14, 2008